Lamotrigine induced Stevens-Johnson Syndrome. A case report

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Case Report

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Background:
Stevens-Johnson Syndrome (SJS) is a severe, life-threatening mucocutaneous disorder, often induced by medications such as lamotrigine. First described in 1922, SJS involves severe conjunctivitis, stomatitis, and purpuric macules. Lamotrigine, an anticonvulsant and mood stabilizer approved by the FDA in 1994, is one of the drugs linked to SJS, especially when dosed too high or escalated too quickly.
We report a case of SJS in an 18-year-old woman with epilepsy who developed symptoms after switching to lamotrigine. Initial symptoms included fever, facial edema, and a painful erythematous rash. On admission to the hospital, the patient presented with a purpuric rash, pustules, and ulcerations, which confirmed SJS.
SJS and toxic epidermal necrolysis (TEN) form a disease spectrum, differing in the extent of skin involvement. While SJS affects less than 10% of body surface area, TEN involves more than 30%. Medications like lamotrigine, phenytoin, and NSAIDs are common triggers. The condition is often preceded by nonspecific symptoms such as fever and discomfort.
Treatment strategies focus on withdrawing the causative drug and providing supportive care. Corticosteroids, intravenous immunoglobulins, and cyclosporine have shown varying degrees of efficacy, although evidence on their effectiveness remains debated. Early intervention is critical due to the high mortality rates of SJS/TEN, estimated between 34-50%.

Keywords: Stevens-Johnson Syndrome, Lamotrigine

Stevens-Johnson syndrome was first described in 1922 as an acute mucocutaneous syndrome in two young children. The condition was characterized by severe purulent conjunctivitis, severe stomatitis with extensive mucosal necrosis, and purpuric macules. It became known as Stevens-Johnson syndrome and was recognized as a serious mucocutaneous disease with a protracted course and a potentially fatal outcome that was, in most cases, drug-induced and must be distinguished from erythema multiforme major.[1,2,3]

In 1993, Bastuji-Garin et al proposed that erythema multiforme major and Stevens-Johnson syndrome were different disorders. Because of this, the term erythema multiforme major should not be used to describe Stevens-Johnson syndrome, as they are separate disorders.[4]

The lamotrigine is an antiepileptic and mood-stabilizing drug approved by the Food and Drug Administration (FDA) in 1994. It is the only antiepileptic approved for the treatment and maintenance of bipolar disorder and one of the few agents with efficacy for depression in patients with bipolar disorder, in addition to being indicated for partial and generalized seizures.[5] Since its approval, it has been reported in the literature that it can cause Stevens-Johnson Syndrome.[6,7,8,9]

It is important to be aware of this condition in order to diagnose and treat it in time given its high morbidity and mortality. A clinical case of Stevens-Johnson Syndrome is reported, treated at the New General Hospital of Gómez Palacio Durango, secondary to the recent intake of lamotrigine in a patient with a history of epilepsy.

Case report

An 18-year-old woman with a history of late surgical puerperium and epilepsy of 2 years of duration on initial treatment with magnesium valproate, which was changed by a private doctor to lamotrigine 100 mg orally every 12 hours four weeks before having started with unquantified fever, accompanied by chills self-medicated with paracetamol; two weeks later, facial and lip edema was added, in addition to a painful erythematous rash with progressive cephalocaudal spread.

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Figure 1. A generalized, bilateral, symmetrical dermatosis, with purpuric rash that spared certain acral areas and islands of normal skin.

Upon admission to the emergency room of our unit with suspected dengue vs systemic lupus erythematosus, complementary studies such as IgM, IgG and NS1 antigen for dengue were requested with negative results. In addition, anti-double-stranded DNA antibodies, antinuclear antibodies and anti-histone antibodies were requested with negative results, ruling out said pathologies.

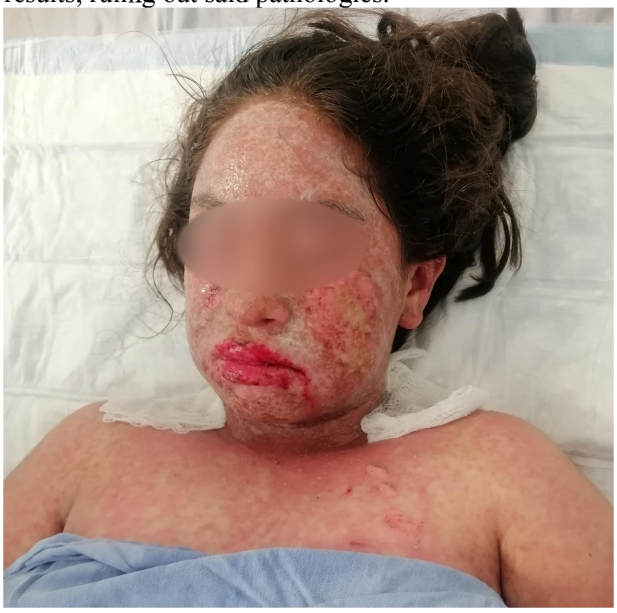

Figure 2. Face and neck with edema and erythema, with countless pustules, ulcerations, bloody and honey-colored crusts on the lips and eyelids.

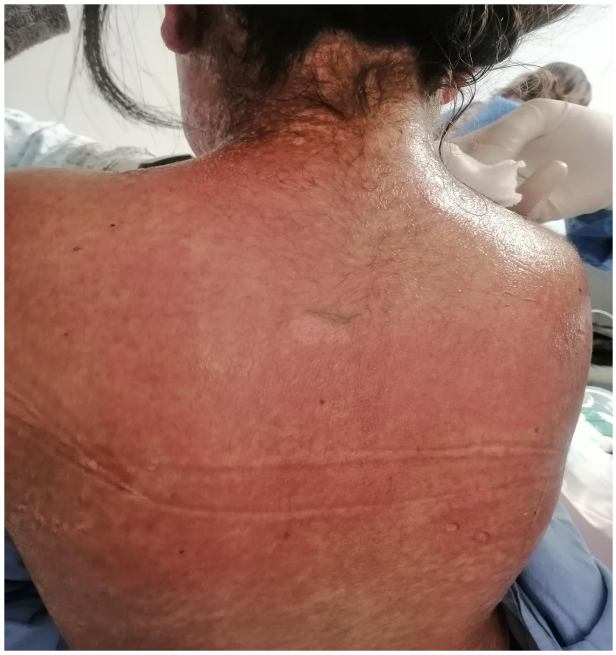

Figure 3. Micro pustules dispersed in the three segments, with an exulcerated body surface area of less than 10%.

A complete blood count was performed with leukocytes of 9460/uL, neutrophils of 6.89, eosinophils of 0.83, hemoglobin of 12.88 g/dL and platelets of 288,000/uL, serum electrolytes within normal parameters, glucose of 113 mg/dL, urea nitrogen of 23. mg/dL, urea of 49.2 mg/dL and creatinine of 0.7 mg/dL. A blood culture was also requested, which was without alterations, and a general urine test with abundant bacteria, positive nitrites and proteinuria of 30 mg/dL.

Later, in the hospitalization area, a generalized, bilateral, symmetrical dermatosis was seen, consisting of a purpuric rash that spared certain acral areas and islands of normal skin **(Figure 1)**, in the cephalic segment with involvement of the face and

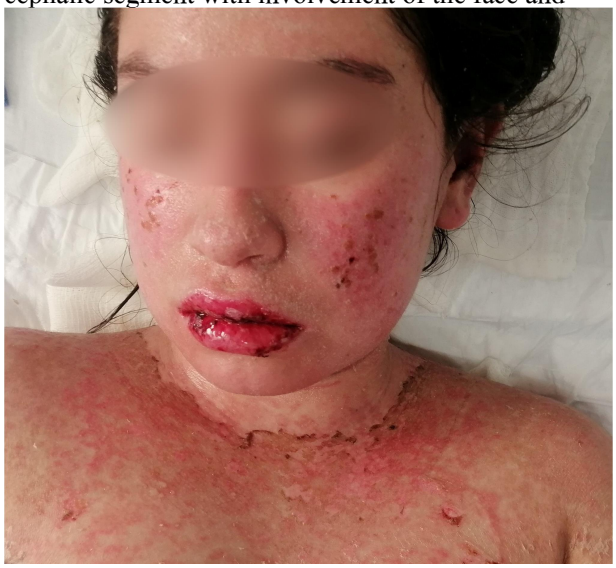

Figure 4. Improvement of lesions with systemic steroid treatment.

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Causative drugs of Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis	
Drug classification	Causative drugs
Antibiotics	Penicilins, cephems, fluoroquinolones, sulfamethoxazole and trimethoprim combination
Xanthine oxidase inhibitor	Allopurinol
Anti-inflammatory drugs	Acetaminophen, loxoprofen, celecoxib, ibuprofen
Antiepileptic drugs	Carbamazepine, lamotrigine, phenytoin, valproic acid
Peptic ulcer agent	Lansoprazole, omeprazole, esomeprazole
Anti-HIV drug	Nevirapine

Table 1. Causative drugs of Stevens-Johnson syndrome and Toxic Epidermal Necrolysis.[10]

neck with edema and erythema, with countless pustules, ulcerations, bloody and honey-colored crusts on the lips and eyelids **(Figure 2)**, with stomatitis of the same characteristics. In addition, she presented micro pustules dispersed in the three segments, with an exulcerated body surface area of less than 10% **(Figure 3)**, establishing the clinical diagnosis of Stevens-Johnson Syndrome.

Discussion

Stevens–Johnson syndrome and toxic epidermal necrolysis are severe, life-threatening mucocutaneous reactions characterized by blisters and extensive skin detachment.[10]

Stevens-Johnson syndrome and toxic epidermal necrolysis are considered part of the same disease spectrum and are differentiated by the extent of skin involved. Stevens-Johnson syndrome is characterized by less than 10% of body surface area involvement, toxic epidermal necrolysis is characterized by greater than 30% of body surface area involvement, and Stevens-Johnson syndrome/toxic epidermal necrolysis overlap has 10-30% of body surface area involvement.[4]

A USA-based study analyzing nationwide inpatient records from 2009 to 2012 calculated an incidence per million inhabitants of 8.61 to 9.69 for Stevens Johnson Syndrome, 1.46 to 1.84 for SJS/TEN, and 1.58 to 2.26 for Toxic Epidermal Necrolysis.[11]

In another study in northern Italy, Stevens Johnson Syndrome/Toxic Epidermal Necrolysis had an overall incidence of 1.4 cases per million population.[12] The incidence of SJS/TEN in a European population-based study in West Germany and Berlin between 1990-1992 was 1.89 per million population.[13] Frey et al. reported an incidence of 5.76 cases of SJS/TEN per million persons per year in the UK from 1995–2013.[14]

Risk factors for SCORTEN	
Risk factors	Illustration
Age	Age >40 years
Tachycardia	Heart rate >120 beats/min
Malignancy	Presence of cancer or hematologic malignancy
Epidermal detachment	Epidermal detachment area involving body surface area >10%
Serum urea	Blood urea nitrogen >28 mg/dL
Serum glucose	Blood glucose >252 mg/dL (14 mmol/L)
Bicarbonate	Bicarbonate <20 mmol/L
Mortality rate for SCORTEN	
Number of risk factors	Mortality rate (%)
0-1	3.2%
2	12.1%
3	35.3%
4	58.3%
>5	90.0%

Table 2. Risk factors for SCORTEN and mortality rates.[30] SCORTEN: Severity of illness score for toxic epidermal necrolysis.

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Risk factors for CRISTEN		
Number	Parameter	Detailed Definition
1	Age	Age over 65 years
2	Epidermal detachment	Epidermal detachment of >10% of body surface area
3	Malignant neoplasm	Active phase
4	Diabetes Mellitus	Under treatment with medication
5	Renal impairment	Chronic kidney disease
6	Bacterial infection	Pneumonia, sepsis, and urinary tract infection
7	Cardiac disease	Heart failure, valvular disease, arrhythmias, aortic aneurysms, angina, atrial and ventricular septal defects, and hypertension under treatment
8	Drugs	Antibiotics in the culprit drugs
9	Mucosal damage	Mucosal damage affecting all three of ocular, bucal, and genital mucosa
10	Systemic corticosteroid therapy before the onset of SJS/TEN	Regardless of dose or duration of administration

Table 3. Clinical risk score for toxic epidermal necrolysis (CRISTEN[31]; SJS: Stevens-Johnson Syndrome; TEN: Toxic Epidermal Necrolysis.

Approximately 80% of SJS/TEN cases in adults are associated with medications.[15] Multiple drugs include but not limited to lamotrigine, carbamazepine, nevirapine, phenytoin, and NSAIDs especially celecoxib and ibuprofen.[16] The allopurinol, when prescribed at doses of 200 mg or more, also increases the risk of SJS.[17]

The list of drugs most frequently associated with Stevens Johnson syndrome is listed in Table 1.
A known risk factor for developing SJS/TEN is HIV infection. The risk of developing SJS/TEN was increased 100-fold in HIV-positive patients according to reports from the Ontario HIV Treatment Network.[18] In an observational study in South Africa of SJS/TEN, HIV infection was shown to be the major factor associated with a higher risk of fatal outcome. The highest risk was found in patients with HIV/tuberculosis co-infection.[19]

Other primary diagnoses that are associated with the development of secondary SJS include various subtypes of sepsis, active cancers, acute kidney disease, multiple myeloma, leukemia, non-Hodgkin lymphoma, mycoplasma infection, pneumonia, epilepsy, and lupus.[20,21] Furthermore, herpes simplex virus has been recognized in several cases of SJS, especially in children.[22]

On a systemic review of 122 randomized trials including 18,698 patients, a risk to develop SJS/TEN after use of lamotrigine of 0.04% (8 of 18,698 patients) was calculated by Bloom et al.[23] The risk of SJS and TEN with lamotrigine is dose-dependent, with a high starting dose and rapid dose escalation increasing the risk of SJS and TEN.[24]

In addition, caution should be used when prescribing valproic acid with lamotrigine because valproic acid inhibits lamotrigine glucuronidation and decreases its clearance which increases the risk of SJS and TEN.[25]

The clinical features of Stevens Johnson syndrome may begin with nonspecific symptoms such as fever, stinging eyes, discomfort upon swallowing and cough, which usually precede the appearance of skin manifestations by a few days.[2,26,27.] The first sites of skin involvement are the presternal region of the trunk and face, but also the palms of the hands and soles of the feet. Involvement of the oral, genital and/or ocular mucosa occurs in more than 80-90% of patients, and in some cases also of the respiratory and gastrointestinal tracts.[2,26.] Oral involvement is the most frequent, with mucositis and ulceration occurring in up to 100% of cases.[29]

Actually, subsequent cutaneous and mucosal involvement is universal and may appear as erythematous macules or atypical target lesions on the trunk that progress to confluent areas of erythema with dark centers, flaccid blisters with a positive Nikolsky sign, and sheets of denuded epidermis.[26,28.] Gynecological involvement also varies in severity but is seen in up to 77% of female patients.[29]

Given that SJS/TEN has a high mortality rate, estimated to be between 34 and 50% globally, the most critical clinical assessments are severity and

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mortality risk.[30,31] The Severity and mortality risk of SJS/TEN can be estimated with several validated tools.

The severity-of-illness score for toxic epidermal necrolysis (SCORTEN) is widely used to predict mortality in SJS/TEN patients.[32] SCORTEN should be assessed within the first 24 h of admission and re-evaluated on day 3. This scoring system is based on seven independent risk factors: age, malignancy, tachycardia, percentage of epidermal detachment, serum urea, serum glucose, and bicarbonate levels; and the presence of more risk factors correlates with higher mortality rates. Risk factors for SCORTEN and mortality rates are listed in Table 2.

In 2023, Natsumi Hama et al. proposed a new scoring system to predict mortality in Stevens-Johnson syndrome and toxic epidermal necrolysis called the Clinical Risk Score for TEN (CRISTEN), which predicts early stage mortality using only clinical information, without requiring laboratory data. CRISTEN includes 10 risk factors such as age, percentage of epidermal detachment, use of antibiotics as causative agents, systemic corticosteroid therapy before onset, and mucosal involvement affecting the ocular, buccal, and genital areas. Underlying conditions such as renal failure, diabetes, cardiovascular disease, malignancies and bacterial infections are also taken into account. CRISTEN has shown statistically comparable results to previous systems.[33] The Clinical Risk Score for TEN (CRISTEN) is described in table 3.

There are other validated tools such as the revision of SCORTEN (ReSCORTEN); and the age, bicarbonate, cancer, dialysis, and 10% body surface area risk model (ABCD-10).

Revision of SCORTEN (Re-SCORTEN) for mortality prognosis was proposed by Koh et al, adding red blood cell distribution width to the hemoglobin ratio (RHR), which can be determined from a basic complete blood count. The authors incorporated RHR into SCORTEN by adding a value of 2 for patients with RHR > 1.19, leading to significantly higher prognostic accuracy.[34]

ABCD-10 is a risk prediction model for severity and mortality that uses five indicators (age > 50 years, body surface area > 10%, serum bicarbonate < 20 mmol/L, active cancer, and prior dialysis). This differs from SCORTEN by increasing the weight of cancer on prognosis and by including history of prior dialysis instead of only current kidney function.[35] However, this model has been found to be inferior to SCORTEN at mortality prediction.[36]

There are other ways to determine the severity of this pathology and some laboratory values have emerged as possible markers of severity. These include lactate dehydrogenase, creatine kinase, interleukin-15 and granulysin, all four of which directly correlate with body area involvement.[37,38,39,40]

There are no standard diagnostic criteria for SJS/TEN, diagnosis is usually clinical taking into account the presence of macular target lesions, involvement of two mucosae, recent drug exposure and corresponding histopathology are all indicative. Histopathology is usually not required for the diagnosis of SJS-TEN. Clinical differentiation between SJS and TEN should always be considered and is based on body surface involvement, specifically detached lesions, as mentioned previously. Pseudo-Nikolsky and Asboe Hansen signs can be elicited in most of the cases. However, it should be noted that Nikolsky's sign is not specific to SSJ/TEN. [2,15,41]

Histologically, SJS/TEN exhibits keratinocyte necrosis ranging from partial to full thickness (established lesions), with scant perivascular lymphohistiocytic inflammation. Alternatives to standard processing include frozen section biopsy, Tzanck smear, and “jelly roll,” in which the roof of a fresh blister is submitted for frozen section processing.[42]

Differential diagnosis of SJS/TEN should be considered with erythema multiforme exudative major, autoimmune blistering diseases (e.g., linear IgA dermatosis, epidermolysis bullosa acquisita), autoimmune diseases (e.g., bullous lupus erythematosus), staphylococcal scalded skin syndrome (SSSS), and generalized fixed bullous drug eruption, as well as acute generalized exanthematous pustulosis (AGEP). Differential diagnosis of overlapp diseases, such as AGEP/epidermal necrolysis, and combinations with preexisting diseases, like systemic lupus erythematosus, may be problematic as they may be clinically indistinguishable from SJS/TEN.[43]

The optimal therapeutic strategy for SJS/TEN remains a subject of debate.[44] In 2016, UK guidelines emphasized the prioritization of culprit drug withdrawal and purchasing intensive supportive care over systemic treatment due to the lack of evidence supporting the benefits.[45] However, some studies have reported benefits with the treatment of systemic corticosteroids, intravenous immunoglobulins, cyclosporine, TNF-α antagonists (infliximab and etanercept), and plasmapheresis.[46,47]

Comprehensive analyses and systematic reviews have not shown a survival benefit with the use of systemic corticosteroids[31] However, recent investigations suggested a beneficial effect of corticosteroid therapy. A European multicenter retrospective study, along with recent meta-analysis of observational studies, indicated positive effects of corticosteroids.[47,48] Actually, a recent survey in Japan showed that the ratio of expected to observed mortality, calculated using SCORTEN score, was

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lowest with high-dose of corticosteroid therapy, followed by steroid pulse therapy.[49]

An observational study found that early administration of steroid pulse therapy reduces mortality without increasing the risk of infection[50], and there is a report that steroid pulse therapy early in the disease may prevent ocular complications.[51]

In fact, our patient was treated with intravenous corticosteroids, specifically methylprednisolone at decreasing doses starting with a dose of 125 mg every 6 hours for two consecutive days, then the same dose every 8 hours for 1 day, 125 mg every 12 hours and finally 125 mg once a day, in addition to his supportive treatment with good results and improvement of the lesions.

Regarding intravenous immunoglobulin, it has been previously administered for cases of Stevens Johnson Syndrome and Toxic Epidermal Necrolysis and a recent meta-analysis has shown that high-dose IVIg (<2 g/kg) has a beneficial effect in reducing mortality from SJS/TEN. Even the combination with corticosteroids instead of IVIg monotherapy has shown better results regarding the prognosis of these pathologies.[52,53]

Plasmapheresis works by removing pathogens from the patient's bloodstream, including metabolites, drugs, and disease-induced cytokines or chemokines. There is one report that plasmapheresis may be an effective treatment in patients with Stevens Johnson syndrome and toxic epidermal necrolysis.[54] However, more research is needed.

The cyclosporine, a calcineurin inhibitor, has demonstrated therapeutic efficacy in the treatment of Stevens-Johnson syndrome/toxic epidermal necrolysis. This agent modulates T-cell-mediated cytotoxicity and inhibits key molecules such as FasL, nuclear factor kB, and TNF-α. A meta-analysis showed decreased mortality with the use of cyclosporine.[55]

TNF-α inhibitors have been used in some cases of SJS/TEN and have shown beneficial effects because TNF is associated with keratinocyte death. There are case reports of infliximab being effective in Stevens Johnson Syndrome and Toxic Epidermal Necrolysis.[56] In addition, there is a multicenter observational study that demonstrated the efficacy of combined therapy with etanercept and systemic corticosteroids.[57]

Conclusion

Stevens-Johnson syndrome (SJS) is a severe and potentially fatal reaction involving the skin and mucous membranes, usually induced by drugs, such as lamotrigine. Its early diagnosis is crucial to reduce morbidity and mortality, given its rapid evolution and the complications it can generate. Although its incidence is low, the identification of risk factors such as the use of certain drugs and underlying diseases are essential for its management. Treatment is mainly based on discontinuation of the causative drug and intensive support, with additional options such as intravenous corticosteroids and intravenous immunoglobulin, although evidence on their efficacy varies. Prompt medical intervention is key to improve outcomes, especially when assessment tools such as SCORTEN are used to predict severity and mortality risk.

Conflicts of interests

There was no conflict of interest during the study, and it was not funded by any organization.

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References

1. STEVENS AM, JOHNSON FC. A NEW ERUPTIVE FEVER ASSOCIATED WITH STOMATITIS AND OPHTHALMIA: REPORT OF TWO CASES IN CHILDREN. Am J Dis Child. 1922;24(6):526–533. doi:10.1001/archpedi.1922.04120120077005
2. Harr, T., French, L.E. Toxic epidermal necrolysis and Stevens-Johnson syndrome. Orphanet J Rare Dis 5, 39 (2010). https://doi.org/10.1186/1750-1172-5-39
3. THOMAS BA. The so-called Stevens-Johnson syndrome. Br Med J. 1950 Jun 17;1(4667):1393-7. doi: 10.1136/bmj.1.4667.1393. PMID: 15426760; PMCID: PMC2038151.
4. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau J. Clinical Classification of Cases of Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome, and Erythema Multiforme. Arch Dermatol. 1993;129(1):92–96. doi:10.1001/archderm.1993.01680220104023
5. Stahl, Stephen M. "A rash proposal for psychopharmacologists treating bipolar disorder: become an amateur dermatologist; Rashes are associated with several mood stabilizers, including lamotrigine but also valproic acid, carbamazepine, oxcarbazepine, and zonisamide." Psychopharmacology Educational Updates, vol. 33, no. 6, June 2005, pp. S6+. Gale OneFile: Health and Medicine, link.gale.com/apps/doc/A133671965/HRCA?u=txshracd2618&sid=bookmark-HRCA&xid=00ad15cb. Accessed 9 Dec. 2024.
6. Yapici AK, Fidanci MK, Kilic S, Balamtekin N, Mutluay Arslan M, Yavuz ST, Kalman S. Stevens-Johnson Syndrome triggered by a combination of clobazam, lamotrigine and valproic acid in a 7-year-old child. Ann Burns Fire Disasters. 2014 Sep 30;27(3):121-5. PMID: 26170788; PMCID: PMC4441308.
7. Levi N, Bastuji-Garin S, Mockenhaupt M, Roujeau JC, Flahault A, Kelly JP, Martin E, Kaufman DW, Maison P. Medications as risk factors of Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a pooled analysis. Pediatrics. 2009 Feb;123(2):e297-304. doi: 10.1542/peds.2008-1923. Epub 2009 Jan 19. PMID: 19153164.

8. Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. Neurology. 2005 Apr 12;64(7):1134-8. doi: 10.1212/01.WNL.0000156354.20227.F0. PMID: 15824335.
9. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavinck JN, Sidoroff A, Schneck J, Roujeau JC, Flahault A. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Invest Dermatol. 2008 Jan;128(1):35-44. doi: 10.1038/sj.jid.5701033. Epub 2007 Sep 6. PMID: 17805350.
10. Hasegawa A, Abe R. Stevens-Johnson syndrome and toxic epidermal necrolysis: Updates in pathophysiology and management. Chin Med J (Engl). 2024 Oct 5;137(19):2294-2307. doi: 10.1097/CM9.0000000000003250. Epub 2024 Sep 5. PMID: 39238098; PMCID: PMC11441865.
11. Hsu DY, Brieva J, Silverberg NB, Silverberg JI. Morbidity and Mortality of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in United States Adults. J Invest Dermatol. 2016 Jul;136(7):1387-1397. doi: 10.1016/j.jid.2016.03.023. Epub 2016 Mar 30. PMID: 27039263.
12. Diphoorn J, Cazzaniga S, Gamba C, Schroeder J, Citterio A, Rivolta AL, Vighi GD, Naldi L; REACT-Lombardia study group. Incidence, causative factors and mortality rates of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in northern Italy: data from the REACT registry. Pharmacoepidemiol Drug Saf. 2016 Feb;25(2):196-203. doi: 10.1002/pds.3937. Epub 2015 Dec 21. PMID: 26687641.
13. Rzany B, Mockenhaupt M, Baur S, Schröder W, Stocker U, Mueller J, Holländer N, Bruppacher R, Schöpf E. Epidemiology of erythema exsudativum multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis in Germany (1990-1992): structure and results of a population-based registry. J Clin Epidemiol. 1996 Jul;49(7):769-73. doi: 10.1016/0895-4356(96)00035-2. PMID: 8691227.
14. Frey N, Jossi J, Bodmer M, Bircher A, Jick SS, Meier CR, Spoendlin J. The Epidemiology of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in the UK. J Invest Dermatol. 2017 Jun;137(6):1240-1247. doi: 10.1016/j.jid.2017.01.031. Epub 2017 Feb 12. PMID: 28202399.
15. Shah H, Parisi R, Mukherjee E, Phillips EJ, Dodiuk-Gad RP. Update on Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Diagnosis and Management. Am J Clin Dermatol. 2024 Nov;25(6):891-908. doi: 10.1007/s40257-024-00889-6. Epub 2024 Sep 15. PMID: 39278968; PMCID: PMC11511757.
16. Edinoff AN, Nguyen LH, Fitz-Gerald MJ, Crane E, Lewis K, Pierre SS, Kaye AD, Kaye AM, Kaye JS, Kaye RJ, Gennuso SA, Varrassi G, Viswanath O, Urits I. Lamotrigine and Stevens-Johnson Syndrome Prevention. Psychopharmacol Bull. 2021 Mar 16;51(2):96-114. PMID: 34092825; PMCID: PMC8146560.
17. Halevy S, Ghislain PD, Mockenhaupt M, Fagot JP, Bouwes Bavinck JN, Sidoroff A, Naldi L, Dunant A, Viboud C, Roujeau JC; EuroSCAR Study Group. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. J Am Acad Dermatol. 2008 Jan;58(1):25-32. doi: 10.1016/j.jaad.2007.08.036. Epub 2007 Oct 24. PMID: 17919772.
18. Mittmann N, Knowles SR, Koo M, Shear NH, Rachlis A, Rourke SB. Incidence of toxic epidermal necrolysis and Stevens-Johnson Syndrome in an HIV cohort: an observational, retrospective case series study. Am J Clin Dermatol. 2012 Feb 1;13(1):49-54. doi: 10.2165/11593240-000000000-00000. PMID: 22145749.
19. Kannenberg SM, Jordaan HF, Koegelenberg CF, Von Groote-Bidlingmaier F, Visser WI. Toxic epidermal necrolysis and Stevens-Johnson syndrome in South Africa: a 3-year prospective study. QJM. 2012 Sep;105(9):839-46. doi: 10.1093/qjmed/hcs078. Epub 2012 Apr 28. PMID: 22543685.
20. Hsu DY, Brieva J, Silverberg NB, Paller AS, Silverberg JI. Pediatric Stevens-Johnson syndrome and toxic epidermal necrolysis in the United States. J Am Acad Dermatol. 2017 May;76(5):811-817.e4. doi: 10.1016/j.jaad.2016.12.024. Epub 2017 Mar 9. PMID: 28285784; PMCID: PMC5502094.
21. Mulvey JM, Padowitz A, Lindley-Jones M, Nickels R. Mycoplasma pneumoniae associated with Stevens Johnson syndrome. Anaesth Intensive Care. 2007 Jun;35(3):414-7. doi: 10.1177/0310057X0703500317. PMID: 17591139.
22. Forman R, Koren G, Shear NH. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a review of 10 years' experience. Drug Saf. 2002;25(13):965-72. doi: 10.2165/00002018-200225130-00006. PMID: 12381216.
23. Bloom R, Amber KT. Identifying the incidence of rash, Stevens-Johnson syndrome and toxic epidermal necrolysis in patients taking lamotrigine: a systematic review of 122 randomized controlled trials. An Bras Dermatol. 2017 Jan-Feb;92(1):139-141. doi: 10.1590/abd1806-4841.20175070. PMID: 28225977; PMCID: PMC5312199.
24. Parveen S, Javed MA. Stevens Johnson Syndrome associated with Lamotrigine. Pak J Med Sci. 2013 Nov;29(6):1450-2. doi: 10.12669/pjms.296.4385. PMID: 24550973; PMCID: PMC3905385.
25. Rzany B, Correia O, Kelly JP, Naldi L, Auquier A, Stern R. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. Study Group of the International Case Control Study on Severe Cutaneous Adverse Reactions. Lancet. 1999 Jun 26;353(9171):2190-4. doi: 10.1016/s0140-6736(98)05418-x. PMID: 10392983.
26. Frantz R, Huang S, Are A, Motaparthi K. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Review of Diagnosis and Management. Medicina (Kaunas). 2021 Aug 28;57(9):895. doi: 10.3390/medicina57090895. PMID: 34577817; PMCID: PMC8472007.
27. Hasegawa A, Abe R. Recent advances in managing and understanding Stevens-Johnson syndrome and toxic epidermal necrolysis. F1000Res. 2020 Jun 16;9:F1000 Faculty Rev-612. doi: 10.12688/f1000research.24748.1. PMID: 32595945; PMCID: PMC7308994.
28. Grünwald P, Mockenhaupt M, Panzer R, Emmert S. Erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis - diagnosis and treatment. J Dtsch Dermatol Ges. 2020 Jun;18(6):547-553. doi: 10.1111/ddg.14118. Epub 2020 May 29. PMID: 32469468.
29. Shanbhag SS, Chodosh J, Fathy C, Goverman J, Mitchell C, Saeed HN. Multidisciplinary care in Stevens-Johnson syndrome. Ther Adv Chronic Dis. 2020 Apr 28;11:2040622319894469. doi:

10.1177/2040622319894469. PMID: 32523661; PMCID: PMC7236394.

30. Kim HI, Kim SW, Park GY, Kwon EG, Kim HH, Jeong JY, Chang HH, Lee JM, Kim NS. Causes and treatment outcomes of Stevens-Johnson syndrome and toxic epidermal necrolysis in 82 adult patients. Korean J Intern Med. 2012 Jun;27(2):203-10. doi: 10.3904/kjim.2012.27.2.203. Epub 2012 May 31. PMID: 22707893; PMCID: PMC3372805.
31. Sekula P, Dunant A, Mockenhaupt M, Naldi L, Bouwes Bavinck JN, Halevy S, Kardaun S, Sidoroff A, Liss Y, Schumacher M, Roujeau JC; RegiSCAR study group. Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. J Invest Dermatol. 2013 May;133(5):1197-204. doi: 10.1038/jid.2012.510. Epub 2013 Feb 7. PMID: 23389396.
32. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol. 2000 Aug;115(2):149-53. doi: 10.1046/j.1523-1747.2000.00061.x. PMID: 10951229.
33. Hama N, Sunaga Y, Ochiai H, Kokaze A, Watanabe H, Kurosawa M, Azukizawa H, Asada H, Watanabe Y, Yamaguchi Y, Aihara M, Mizukawa Y, Ohyama M, Hashizume H, Nakajima S, Nomura T, Kabashima K, Tohyama M, Hasegawa A, Takahashi H, Mieno H, Ueta M, Sotozono C, Niihara H, Morita E, Brüggen MC, Feingold IM, Jeschke MG, Dodiuk-Gad RP, Oppel EM, French LE, Chen WT, Chung WH, Chu CY, Kang HR, Ingen-Housz-Oro S, Nakamura K, Sueki H, Abe R. Development and Validation of a Novel Score to Predict Mortality in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: CRISTEN. J Allergy Clin Immunol Pract. 2023 Oct;11(10):3161-3168.e2. doi: 10.1016/j.jaip.2023.07.001. Epub 2023 Jul 8. Erratum in: J Allergy Clin Immunol Pract. 2024 Jul;12(7):1950. doi: 10.1016/j.jaip.2024.06.006. PMID: 37429419.
34. Koh HK, Fook-Chong SMC, Lee HY. Improvement of Mortality Prognostication in Patients With Epidermal Necrolysis: The Role of Novel Inflammatory Markers and Proposed Revision of SCORTEN (Re-SCORTEN). JAMA Dermatol. 2022 Feb 1;158(2):160-166. doi: 10.1001/jamadermatol.2021.5119. PMID: 34935871; PMCID: PMC8696686.
35. Noe MH, Rosenbach M, Hubbard RA, Mostaghimi A, Cardones AR, Chen JK, Cotliar J, Davis MDP, Dominguez A, Fox LP, Hughey LC, Kaffenberger BH, Kroshinsky D, Kwong BY, Miller DD, Musiek A, Ortega-Loayza AG, Sharon VR, Shinkai K, Summers EM, Wanat KA, Wetter DA, Worswick S, Margolis DJ, Gelfand JM, Micheletti RG. Development and Validation of a Risk Prediction Model for In-Hospital Mortality Among Patients With Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis-ABCD-10. JAMA Dermatol. 2019 Apr 1;155(4):448-454. doi: 10.1001/jamadermatol.2018.5605. Erratum in: JAMA Dermatol. 2019 Sep 1;155(9):1090. doi: 10.1001/jamadermatol.2019.2200. Erratum in: JAMA Dermatol. 2019 Sep 1;155(9):1090. doi: 10.1001/jamadermatol.2019.2835.. Kroshinsky, Daniel [corrected to Kroshinsky, Daniela]. PMID: 30840032; PMCID: PMC6459085.
36. Duplisea MJ, Roberson ML, Chrisco L, Strassle PD, Williams FN, Ziemer CM. Performance of ABCD-10 and SCORTEN mortality prediction models in a cohort of patients with Stevens-Johnson syndrome/toxic epidermal necrolysis. J Am Acad Dermatol. 2021 Oct;85(4):873-877. doi: 10.1016/j.jaad.2021.04.082. Epub 2021 Apr 30. PMID: 33940101.
37. Yun SJ, Choi MS, Piao MS, Lee JB, Kim SJ, Won YH, Lee SC. Serum lactate dehydrogenase is a novel marker for the evaluation of disease severity in the early stage of toxic epidermal necrolysis. Dermatology. 2008;217(3):254-9. doi: 10.1159/000148255. Epub 2008 Jul 30. PMID: 18667824.
38. Caux F, Chosidow O, Philippon C, Roujeau JC, Revuz J. Increased serum and blister fluid levels of creatine kinase in patients with toxic epidermal necrolysis. Br J Dermatol. 1994 Mar;130(3):337-41. doi: 10.1111/j.1365-2133.1994.tb02930.x. PMID: 8148275.
39. Su SC, Mockenhaupt M, Wolkenstein P, Dunant A, Le Gouvello S, Chen CB, Chosidow O, Valeyrie-Allanore L, Bellon T, Sekula P, Wang CW, Schumacher M, Kardaun SH, Hung SI, Roujeau JC, Chung WH. Interleukin-15 Is Associated with Severity and Mortality in Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis. J Invest Dermatol. 2017 May;137(5):1065-1073. doi: 10.1016/j.jid.2016.11.034. Epub 2016 Dec 21. PMID: 28011147.
40. Abe R, Yoshioka N, Murata J, Fujita Y, Shimizu H. Granulysin as a marker for early diagnosis of the Stevens-Johnson syndrome. Ann Intern Med. 2009 Oct 6;151(7):514-5. doi: 10.7326/0003-4819-151-7-200910060-00016. PMID: 19805776.
41. Kumar, Rajesh; Das, Anupam1; Das, Sudip2. Management of Stevens-Johnson Syndrome-Toxic Epidermal Necrolysis: Looking Beyond Guidelines!. Indian Journal of Dermatology 63(2):p 117-124, Mar–Apr 2018. | DOI: 10.4103/ijd.IJD_583_17.
42. Noe MH, Micheletti RG. Diagnosis and management of Stevens-Johnson syndrome/toxic epidermal necrolysis. Clin Dermatol. 2020 Nov-Dec;38(6):607-612. doi: 10.1016/j.clindermatol.2020.06.016. Epub 2020 Jun 30. PMID: 33341195.
43. Lerch M, Mainetti C, Terziroli Beretta-Piccoli B, Harr T. Current Perspectives on Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. Clin Rev Allergy Immunol. 2018 Feb;54(1):147-176. doi: 10.1007/s12016-017-8654-z. PMID: 29188475.
44. White KD, Abe R, Ardern-Jones M, Beachkofsky T, Bouchard C, Carleton B, Chodosh J, Cibotti R, Davis R, Denny JC, Dodiuk-Gad RP, Ergen EN, Goldman JL, Holmes JH 4th, Hung SI, Lacouture ME, Lehloenya RJ, Mallal S, Manolio TA, Micheletti RG, Mitchell CM, Mockenhaupt M, Ostrov DA, Pavlos R, Pirmohamed M, Pope E, Redwood A, Rosenbach M, Rosenblum MD, Roujeau JC, Saavedra AP, Saeed HN, Struewing JP, Sueki H, Sukasem C, Sung C, Trubiano JA, Weintraub J, Wheatley LM, Williams KB, Worley B, Chung WH, Shear NH, Phillips EJ. SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation. J Allergy Clin Immunol Pract. 2018 Jan-Feb;6(1):38-69. doi: 10.1016/j.jaip.2017.11.023. PMID: 29310768; PMCID: PMC5857362.
45. Creamer D, Walsh SA, Dziewulski P, Exton LS, Lee HY, Dart JK, Setterfield J, Bunker CB, Ardern-Jones MR, Watson KM, Wong GA, Philippidou M, Vercueil A, Martin RV, Williams G, Shah M, Brown D, Williams P, Mohd Mustapa MF, Smith CH. U.K. guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016. Br J Dermatol. 2016 Jun;174(6):1194-227. doi: 10.1111/bjd.14530. PMID: 27317286.
46. Schneider JA, Cohen PR. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Concise Review

with a Comprehensive Summary of Therapeutic Interventions Emphasizing Supportive Measures. Adv Ther. 2017 Jun;34(6):1235-1244. doi: 10.1007/s12325-017-0530-y. Epub 2017 Apr 24. PMID: 28439852; PMCID: PMC5487863.

47. Zimmermann S, Sekula P, Venhoff M, Motschall E, Knaus J, Schumacher M, Mockenhaupt M. Systemic Immunomodulating Therapies for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Systematic Review and Meta-analysis. JAMA Dermatol. 2017 Jun 1;153(6):514-522. doi: 10.1001/jamadermatol.2016.5668. PMID: 28329382; PMCID: PMC5817620.
48. Schneck J, Fagot JP, Sekula P, Sassolas B, Roujeau JC, Mockenhaupt M. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: A retrospective study on patients included in the prospective EuroSCAR Study. J Am Acad Dermatol. 2008 Jan;58(1):33-40. doi: 10.1016/j.jaad.2007.08.039. Epub 2007 Oct 4. PMID: 17919775.
49. Sunaga Y, Kurosawa M, Ochiai H, Watanabe H, Sueki H, Azukizawa H, Asada H, Watanabe Y, Yamaguchi Y, Aihara M, Mizukawa Y, Ohyama M, Hama N, Abe R, Hashizume H, Nakajima S, Nomura T, Kabashima K, Tohyama M, Takahashi H, Mieno H, Ueta M, Sotozono C, Niihara H, Morita E, Kokaze A. The nationwide epidemiological survey of Stevens-Johnson syndrome and toxic epidermal necrolysis in Japan, 2016-2018. J Dermatol Sci. 2020 Dec;100(3):175-182. doi: 10.1016/j.jdermsci.2020.09.009. Epub 2020 Sep 28. PMID: 33046331.
50. Hirahara K, Kano Y, Sato Y, Horie C, Okazaki A, Ishida T, Aoyama Y, Shiohara T. Methylprednisolone pulse therapy for Stevens-Johnson syndrome/toxic epidermal necrolysis: clinical evaluation and analysis of biomarkers. J Am Acad Dermatol. 2013 Sep;69(3):496-8. doi: 10.1016/j.jaad.2013.04.007. PMID: 23957982.
51. Kardaun SH, Jonkman MF. Dexamethasone pulse therapy for Stevens-Johnson syndrome/toxic epidermal necrolysis. Acta Derm Venereol. 2007;87(2):144-8. doi: 10.2340/00015555-0214. PMID: 17340021.
52. Barron SJ, Del Vecchio MT, Aronoff SC. Intravenous immunoglobulin in the treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis: a meta-analysis with meta-regression of observational studies. Int J Dermatol. 2015 Jan;54(1):108-15. doi: 10.1111/ijd.12423. Epub 2014 Apr 2. PMID: 24697283.
53. Tsai TY, Huang IH, Chao YC, Li H, Hsieh TS, Wang HH, Huang YT, Chen CY, Cheng YC, Kuo PH, Huang YC, Tu YK. Treating toxic epidermal necrolysis with systemic immunomodulating therapies: A systematic review and network meta-analysis. J Am Acad Dermatol. 2021 Feb;84(2):390-397. doi: 10.1016/j.jaad.2020.08.122. Epub 2020 Sep 6. PMID: 32898587.
54. Bamichas G, Natse T, Christidou F, Stangou M, Karagianni A, Koukourikos S, Chaidemenos G, Chrysomallis F, Sombolos K. Plasma exchange in patients with toxic epidermal necrolysis. Ther Apher. 2002 Jun;6(3):225-8. doi: 10.1046/j.1526-0968.2002.00409.x. PMID: 12109948.
55. Ng QX, De Deyn MLZQ, Venkatanarayanan N, Ho CYX, Yeo WS. A meta-analysis of cyclosporine treatment for Stevens-Johnson syndrome/toxic epidermal necrolysis. J Inflamm Res. 2018 Mar 28;11:135-142. doi: 10.2147/JIR.S160964. PMID: 29636627; PMCID: PMC5880515.
56. Wojtkiewicz A, Wysocki M, Fortuna J, Chrupek M, Matczuk M, Koltan A. Beneficial and rapid effect of infliximab on the course of toxic epidermal necrolysis. Acta Derm Venereol. 2008;88(4):420-1. doi: 10.2340/00015555-0462. PMID: 18709327.
57. Zhang J, Lu CW, Chen CB, Wang CW, Chen WT, Cheng B, Ji C, Chung WH. Evaluation of Combination Therapy With Etanercept and Systemic Corticosteroids for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Multicenter Observational Study. J Allergy Clin Immunol Pract. 2022 May;10(5):1295-1304.e6. doi: 10.1016/j.jaip.2022.01.038. Epub 2022 Feb 4. PMID: 35131514.

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